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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1627	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,713	SCHELLER ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,17,24-35 and 37-78* is/are pending in the application.

4a) Of the above claim(s) *16,36 and 68-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,17,24-35,37-67,78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 8/7/2009 amending claims 17, 30-34, 37, 51-55, 57, 66, 67 and adding new claim 78. Claims 1-15, 18-23 have been canceled. Claims 16, 17, 24-78 are pending. Claims 16, 36, 68-77 are withdrawn from consideration. Claims 17, 24-35, 37-67, 78 are being examined on the merits herein.

Response to Arguments

Applicants' state that Applicants' may elect to argue to overcome the ODP rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the '699 application issues as a patent. Applicants' arguments regarding the rejection of claims 17-35, 37-67 under U.S.C. 112(1) paragraph and 103(a) rejections have been fully considered. Applicants' amendment of claims necessitated the modified ODP, 112(1) and 103(a) rejections presented in this action. The action is made Final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17, 24-35, 37-67 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-82 of copending Application No. 10/565,699. Although the conflicting claims are not identical, they are not patentably distinct from each other because both teach a method of treating depression comprising administering rotigotine. Claims 17, 24, 25, 37-67 of the instant application teach a method of treating depression comprising administering compounds including rotigotine (elected species) and additional drugs that include antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives. Claims 10-82 of the co-pending application '699 teach a method of treating depression comprising administering rotigotine and additional drugs that include antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and, (8) the quantity of experimentation necessary.

Claims 17, 35, 56, 57-67 are rejected under 35 U.S.C. 112, first paragraph, because specification while demonstrating the suitability of rotigotine as an antidepressant in three animal models (para 0015-18) does not reasonably provide enablement for treating depression in a combination therapy as claimed (claims 35, 58-66) with addition of one or more antidepressants, anxiolytics, sedatives, antipsychotics and anti-migraine agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

(1, 5) The nature of the invention and the breadth of the claims:

The instant claims are directed to a method of treating depression in a mammal comprising administering a compound of formula of claim 14. The dependent claims (35, 58-66) claim administration of additional ingredients such as antidepressants, anxiolytics, sedatives, antipsychotics and anti-migraine agents. The dependent claims then are directed to treatment of various kinds of depression that include somatogenic, psychogenic, endogenous, symptomatic, pharmacogenic etc. Claims 35, 56-65 are very

broad with respect to the addition of another ingredient in the treatment namely antidepressants (from various classes), sedatives, anti-psychotics. anti-migraine and anxiolytics compounds.

(3) The relative skill of those in the art:

The relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training.

(2)/(4) The state of the prior art and the predictability of the art:

The prior art teaches the use of antidepressants in combination therapy. Van der Weide (E J of Pharmacology, 1988, 146, 319-326) teaches N-0437 (rotigotine) enantiomers are very promising candidates for psychotherapeutic use (see Abstract). Timmerman (chapter 9, E J of pharmacology, 181, 1989, 253-60) teaches N-0437 (rotigotine) as an antipsychotic drug. Hrdlicka (Eur Psychiatry, 2002, 17, 484) teaches combination therapy of clozapine (antipsychotic drug) in psychotic depression. The prior art Ranjan et al. (Biol Psychiatry, 1996, 40, 253-58) teaches clozapine in treating psychotic depression. Joffe et al. (Acta Psychiatr Scand, 1997, Jun 95(6), 551-2) teaches adverse event reports of fluoxetine and evidence of a drug interaction between fluoxetine (an antidepressant) and sumatriptan (anti-migraine drug) suggesting that this combination is not entirely free of side-effects and should be used with caution when indicated (see Abstract). There are prior art teachings of rotigotine with other compounds such as COX-2 inhibitors (US 20040034083), CB-1 antagonist (US 20040209861) in the treatment of Parkinson's disease, pramipexole or talipexole (dopamine 3 agonists) for the reduction of excessive food intake (US 20050032843)

However, the prior art or the specification does not teach combination of rotigotine with one or more antidepressants, sedatives, anti-psychotics. anti-migraine and anxiolytics. It is not possible to predict that rotigotine can be combined with other antidepressants, (from various classes), sedatives, anti-psychotics. anti-migraine and anxiolytics compounds in treating depression and be therapeutically effective. Joffe et al. (Acta Psychiatr Scand, 1997, Jun 95(6), 551-2) teaches adverse event reports of fluoxetine and evidence of a drug interaction between fluoxetine (an antidepressant) and sumatriptan (anti-migraine drug) suggesting that this combination is not entirely free of side-effects and should be used with caution when indicated (see Abstract). The document on antidepressants (http://en.wikipedia.org/wiki/Antidepressant) teaches that combination therapy is useful in treating patients for depression and further state that aalthough this may be used in clinical practice, there is little evidence for the relative efficacy or adverse effects of this strategy. The document lists various classes of antidepressants available for the treatment. The reference also teaches all the side effects associated with different classes of the antidepressant family. Accordingly, it is not possible to one having ordinary skill in the art at the time of the invention what combination of rotigotine would have been effective in treating depression with the huge class of antidepressants available and yet to be discovered with more efficacy, less side effects and most importantly with less drug interactions. Preskorn (Antidepressants: Past, Present and Future) teaches that use of antidepressant combinations has become increasingly commonplace in young patients but this strategy is not recommended in the elderly due to the increased potential for orthostatic hypotension and side effects.

Hence it is highly unpredictable what the outcome would be for older patients in antidepressant combination therapy.

(6, 7) The amount of guidance presented and the presence of working examples:

It has been established that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). The specification states that substituted 2-amino tetralin compounds in particular rotigotine, are basically suitable for the treatment of the various forms of depression or for the treatment of affective disorders, in particular depressive episodes, recurrent depressive disorders, cyclothymia and depressive phases in bipolar affective disorders. The specification demonstrates the suitability of rotigotine as an antidepressant in three animal models (para 0015-18). However, the specification does not provide any combination therapy with rotigotine or any of the compounds claimed with any of the additional ingredients claimed in the treatment. The specification does not provide any guidance of how much dosage is effective of each additional antidepressant or sedative or anxiolytic or anti-migraine or anti-psychotic in combination therapy in any of the compounds claimed. The specification does not provide guidance to any adverse or drug interactions that may occur in combining the claimed compounds with other drugs. The specification does not provide any guidance to the dosage regimen to patient specific population as prior art teaches that combination therapy in elderly is not recommended due to the increased potential for orthostatic hypotension

and side effects. In summary, Applicant has provided little guidance beyond what was recognized in the art at the time of filing.

(8) The quantity of experimentation needed:

In order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary. Applicants' have tested rotigotine in animal models for treating depression. Applicants' have not shown a combination therapy of rotigotine with one or more antidepressants, sedatives, anti-psychotics. anti-migraine and anxiolytics in treating depression. Considering the unpredictability of the combination of compounds due to the drug interactions, this would be an arduous and daunting task. It would require undue experimentation to test rotigotine to obtain effective dosage for all set of patient population (including elderly) for treating depression in combination with other drugs. Considering the above-mentioned factors and the fact that there are significant inter-individual variability in using a pharmacological modalities in human subjects and the breadth of the claims; one of ordinary skill in the art would be burdened with undue "experimentation study" to determine which combination would be useful in treating depression disorder. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a subject for depression administering rotigotine in combination therapy as claimed. Genetech, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

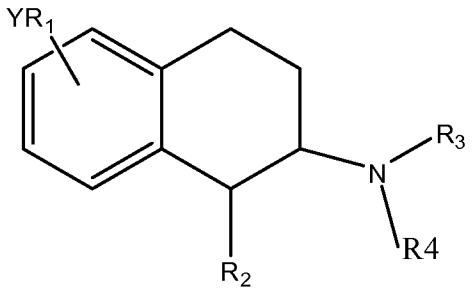
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 17, 24-34, 37-55, 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777).

Weide et al. teaches enantiomers of N-0437 (rotigotine), d2 dopamine receptor agonist stimulates presynaptic dopamine receptors and blocks postsynaptic receptors and these properties make the enantiomers of N-0437 very promising candidates for psychotherapeutic use (see abstract).

Andersson et al. teaches compounds with the formula



Where YR1 is OR1, R2 is H or C1-C3 alkyl, R3 is -CH2- (C3-C8 cycloalkyl); and R4 is hydrogen, C1-Cs alkyl, -CH2- (C3-C4 cycloalkyl), - (CH2)m R5 or-CH2-CH2-X-(CH2) nCH3; where-in n is zero to 3; m is 2 or 3; X is oxygen or sulfur, and R6 is 2-thiophenyl, 3-thiophenyl, phenyl or phenyl substituted by one or two substituents selected from chlorine, bromine, fluorine, C1-C3 alkoxy and C1-C3 alkyl; Furthermore, Andersson teaches that the compounds are useful as a medicament for use as an anxiolytic or anti-depressant. Applicants' claim rotigotine in a method of treating depression (claim 17) and a combination therapy in the dependent claims. Andersson does not teach the claimed compound but the compounds of Andersson have the same core structure as rotigotine.

Sherman in Clinical Psychiatry news reports that pramipexole, a dopamine agonist (affects D2 and D3 receptors) and has been approved for Parkinson's disease has been found to be comparable to fluoxetine in the treatment of depression. The article also states that pramipexole, may be an effective augmentation agent for patients with treatment-resistant depression in combination therapy.

It would have been obvious to one having ordinary skill in the art at the time of the invention that compound such as rotigotine can be used in treating depression from the prior art teachings. Weide et al. teaches rotigotine (N-0437), d2 dopamine receptor

agonist as a very promising candidate for psychotherapeutic use. Andersson et al. teaches structurally similar compounds that have the same core structure as rotigotine and further teach their use in treating depression. Sherman teaches a D2/D3 agonist that has been approved for Parkinson's disease has comparable effects to that of fluoxetine in treating depression. Accordingly, one having ordinary skill in the art would have been motivated to use rotigotine in treating depression in a mammal as the compound is a D2 agonist, has been shown in the prior art to be useful in treating Parkinson's disease and furthermore it is structurally similar to Andersson compounds . It would have been obvious to one having ordinary skill in the art at the time of the invention to have used rotigotine in treating various subtypes of depression namely endogenous, somatogenic, symptomatic, or psychogenic depression. It is known in the art (McAllister-Williams, http://www.netdoctor.co.uk/ diseases/depression/classification_000001.htm) and also from Applicant's specification (para 0028) that endogenous, somatogenic, symptomatic, or psychogenic depression are all subtypes of depression. The document by McAllister Williams teaches that bipolar affective disorder is another subtype of depression and patients with depression have anxiety symptoms. Hence it would have been obvious to one having ordinary skill in the art to administer rotigotine for treating different subtypes of depression or affective disorder such as bipolar affective disorder. It would have been obvious to one having ordinary skill in the art that a drug capable of treating depression would treat the condition irrespective of what the condition is associated with. For example, fluoxetine (SSRI), an antidepressant drug is useful in treating major depression. Fisch (J Clin

Oncol. 2003 May 15;21(10):1937-43) teaches fluoxetine in treating depression (symptomatic depression) in cancer patients and Sobow (Int J of Geriatr Psychiatry, 2001, 1108-1109) teaches the effectiveness of fluoxetine in patients with Alzheimer's disease. It would have been obvious to one having ordinary skill in the art that a drug such as fluoxetine capable of treating depression associated with cancer patients would be effective in treating depression associated with Alzheimer patients. One having ordinary skill in the art would have been motivated to use rotigotine in treating depression in general including the subtypes in achieving similar therapeutic benefits. Weide et al. teaches both enantiomers of rotigotine are very promising candidates for psychotherapeutic use. Hence it would have been obvious to one having ordinary skill in the art to use at least 90% of S enantiomer.

Weide, Andersson et al. and Sherman et al. do not teach the rotigotine dosage regimen, formulation type and administration.

Lauterbach et al. teaches silicone based transdermal therapeutic system comprising two or more silicone adhesives comprising rotigotine and administration of the drug to a patient. The reference teaches daily dosages of 4.5, 9.0 and 13.5 and 18 mg patches can be administered (p 15, lines 5-10).

It would have been obvious to one having ordinary skill in the art at the time of the invention to have formulated as an ointment or a plaster having the active ingredient rotigotine for transdermal administration in treating depression because Lauterbach et al. teaches transdermal therapeutic system comprising rotigotine and further teach the dosage amounts for administration to a patient. Accordingly, one having ordinary skill in

the art would have been motivated to administer the drug transdermally in the claimed amounts because it has been shown in the prior art that such formulation is possible and the drug dosage claimed is a safe amount.

Claims 35, 56, 57, 66, 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of Maj (US 6,255,329).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more antidepressants to rotigotine in treating depression.

Maj teaches treatment of depression in patients comprising administering pramipexole and sertraline (see abstract, col. 4, claim 10). Maj teaches that in combination therapy, the agents can be co-administered separately or as components of a single pharmaceutical dosage form and the drugs can be in different dosage forms (col.2. lines 11-30).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering rotigotine along with one or more antidepressant , sertraline (elected species) in treating depression because of the teachings of Maj. Maj teaches treating depression comprising administering pramipexole (useful for treating

Parkinson's disease) and sertraline. Rotigotine, the elected species is known in the art to treat Parkinson's disease (Lauterbach). One having ordinary skill in the art would have been motivated to use rotigotine for another drug (pramipexole) used in Parkinson's disease in combination with sertraline in treating depression because of expectation of therapeutic benefits, synergistic or additive effects. It would have been obvious to one having ordinary skill in the art at the time of the invention to have administered one of the additional active ingredients in separate dosage forms by the same or different routes at the same or different times because of Maj's teachings. Maj teaches that in treating depression with sertraline the agents can be co-administered separately or as components of a single pharmaceutical dosage form and the drugs can be in different dosage forms. Also, it is well within the skilled medical professional to determine suitable dosing regimens. It would have been customary for an artisan of ordinary skill to determine the optimal dosage of the drug in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of route of delivery, dosage regimens would have been obvious at the time of applicant's invention.

Claims 58, 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of Hrdlicka (Eur Psychiatry, 2002, 17).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more anti-psychotics in treating depression.

Hrdlicka teaches combination of clozapine and maprotiline (a tricyclic antidepressant) in refractory psychotic depression treatment. The reference teaches that clozapine is antipsychotic agent and when administered along with maprotoline to a patient with recurrent depressive disorder.

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 14, such as rotigotine along with an antipsychotic agent, clozapine (elected species) in treating depression because of the teachings of Hrdlicka. Hrdlicka teaches treating depressive disorder comprising administering clozapine and maprotiline (a tricyclic antidepressant). One having ordinary skill in the art would have been motivated to use rotigotine in combination with an anti-psychotic drug such as clozapine because clozapine has been shown to be useful in combination anti-depressant therapy and in expectation of similar therapeutic benefits in combination with rotigotine in treating depression. Also, Timmerman (chapter 9, E J of pharmacology, 181, 1989, 253-60) teaches N-0437 (rotigotine) as an antipsychotic drug. One having ordinary skill in the art would have been motivated to administer one anti-psychotic drug (rotigotine) for clozapine in Hrdlicka's method of treating psychotic depression treatment in expectation of similar and or better therapeutic benefits of treating depression.

Claims 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of Kupfer (Ann Clin Psychiatry, 1999, 11(4), 267-76).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more sedatives in treating depression.

Kupfer teaches that depressed patients often report problems sleeping and epidemiologic evidence suggests that insomnia may precede the onset of depression (see Abstract).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 14, such as rotigotine along with a sedative agent, such as diphenhydramine (elected species) in combination therapy of treating depression because of the teachings of Kupfer. Kupfer teaches that depressed patients often report problems sleeping and it is known in the art that diphenhydramine is a sedative (US 20020177626). One having ordinary skill in the art would have been motivated to use a sedative agent along with an antidepressant in combination therapy in treating depressive patients is to help the patients and improve the quality of sleep in the patients.

Claims 62 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of Zimmerman et al. (Am J Psychiatry 160:504-512, March 2003).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more anxiolytics in treating depression.

Zimmerman teaches that compared to the depressed patients without generalized anxiety disorder, the depressed patients with modified generalized anxiety disorder had higher levels of suicidal ideation; poorer social functioning; a greater frequency of other anxiety disorders, eating disorders, and somatoform disorders (See abstract).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 14, such as rotigotine along with an anxiolytic agent, such as fluspirilene in combination therapy of treating depression because the prior art teachings teach that the depressed patients with modified generalized anxiety disorder had higher levels of suicidal ideation; poorer social functioning; a greater frequency of other anxiety disorders, eating disorders, and somatoform disorders. Fluspirilene is known in the art as an anxiolytic agent (Lehmann,

Neuropsychobiology 1989;21:197-204, Abstract). One having ordinary skill in the art would have been motivated to use an anxiolytic agent along with an antidepressant in combination therapy in treating depressive patients to provide therapeutic benefits for anxiety disorder.

Claims 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of document, Links between Depression and Migraine (5/19/2003).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more anti-migraine in treating depression.

Links between Depression and Migraine document teaches that risk of migraine in individuals with pre-existing major depression was three times higher than in individuals with no history of depression and the risk of major depression in persons with pre-existing migraine was more than fivefold higher than in people with no history of headaches.

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 14, such as rotigotine along with an anti-migraine agent, such as almoptriptan in combination

therapy of treating depression because the prior art teachings teach the connection between migraine and depression. Almotriptan is known in the prior art as an anti-migraine agent (US 20030225002). The document Links between Depression and Migraine teaches that patients with depression had higher risk of migraine. One having ordinary skill in the art would have been motivated to use an anti-migraine agent along with an antidepressant in combination therapy in treating depressive patients to provide therapeutic benefits for migraine.

Response to Arguments

Applicants' argue that enablement exists for one of skill in the art to treat depression by administering a therapeutically effective amount of 5,6,7,8-tetrahydro-6-[propyl- [2-(2-thienyl)ethyl] amino]- 1-naphthol in combination with one or more additional active ingredients having an antidepressive, antipsychotic, sedative, anxiolytic or anti-migraine effect. In response, as stated above, specification teaches the suitability of rotigotine as an antidepressant in three animal models (para 0015-18). Applicants' provided a list of antidepressants, antipsychotics, sedatives etc but have not shown any combination therapy with other agents as claimed. However, the specification does not show at what dosage the therapeutic combination can be made with rotigotine. The specification does not show how to formulate the therapeutic combination because the therapeutic combination can include pharmaceutical compositions comprising rotigotine with a second agent in a single formulation. The specification does not teach at what dosage(s) the combination of a rotigotine with a second agent will be effective for a therapeutic combination. Though pharmacologic properties of the agents listed are

known it is not predictable from the prior art or from the specification how combination of rotigotine with the agents listed will be therapeutically effective combination at all dosage amounts. With no guidance in the specification or in the prior art regarding the dose in a combination therapy, interactions and contraindications of the biological and chemical agents claimed it will be difficult for one having ordinary skill in the art at the time of the invention to predict the outcome of the therapy. Considering the above-mentioned factors and the fact that there are significant inter-individual variability in using a pharmacological modalities in human subjects and the breadth of the claims; one of ordinary skill in the art would be burdened with undue "experimentation study" to determine which combination would be useful in treating depression. Accordingly, the 112(1) scope of enablement for combination therapy of rotigotine with additional agents is maintained.

Applicants' argue that it could not have been predicted from the prior art studies that 5,6,7,8- tetrahydro-6- [propyl- [2-(2-thienyl)ethyl] amino] - 1 -naphthol would be effective in treatment of depression in a mammal and further argue that one of ordinary skill in the art would not predict therapeutic effectiveness of rotigotine in depression just from disclosure of structurally "similar" compounds by Andersson and Sherman. In response, Weide et al. teaches enantiomers of N-0437 (rotigotine), d2 dopamine receptor agonist stimulates presynaptic dopamine receptors and blocks postsynaptic receptors and these properties make the enantiomers of N-0437 very promising candidates for psychotherapeutic use. Psychotherapy is defined as the treatment of mental and emotional disorders through the use of psychological techniques designed

to encourage communication of conflicts and insight into problems, with the goal being relief of symptoms, changes in behavior leading to improved social and vocational functioning, and personality growth. It is well known that depression, anxiety etc are emotional disorders. Hence it would have been obvious to try rotigotine for psychotherapeutic use for one having ordinary skill in the art at the time of the invention from the studies of Weide et al. Andersson teaches compounds that have the same core structure as rotigotine and further teach such compounds to be useful as an anxiolytic or anti-depressant. Sherman reports that pramipexole, a dopamine agonist (affects D2 and D3 receptors) has been found to be comparable to fluoxetine in the treatment of depression and that pramipexole, may be an effective augmentation agent for patients with treatment-resistant depression in combination therapy. In summary, Sherman teaches a D2/D3 dopamine agonist is useful in treating depression and may be an effective augmentation agent in combination therapy. Andersson et al. and Sherman are cited in addition why it would have been obvious to one having ordinary skill in the art at the time of the invention to have tried rotigotine in treating depression as well in a combination therapy with other agents like antidepressants. One having ordinary skill in the art would have been motivated to use rotigotine, a D2 receptor agonist in treating depression because Sherman teaches D2/D3 dopamine agonists are useful in treating depression. One of ordinary skill in the art would have been motivated to use one D2 agonist for another in treating depression in expectation of similar or better therapeutic benefits.

Applicants' argue that antidepressant activity of rotigotine was not known prior to the invention and therefore the cited art fails to teach the invention as claimed in claims 35, 56-67. As stated above, Weide et al. teaches enantiomers of N-0437 (rotigotine), d2 dopamine receptor agonist stimulates presynaptic dopamine receptors and blocks postsynaptic receptors and these properties make the enantiomers of N-0437 very promising candidates for psychotherapeutic use. It is well known that depression, anxiety etc are emotional disorders and hence it would have been obvious to try rotigotine for psychotherapeutic use for one having ordinary skill in the art at the time of the invention from the studies of Weide et al. It is well known in the art at the time of the invention that combination therapy exists for the treatment of depression with the addition of other antidepressant agents in expectation of synergistic effects between two agents that may permit lower dosing of each agent (relative to the recommended doses) to get effective treatment. Hence it would have been obvious to one having ordinary skill in the art at the time of the invention to have used rotigotine in a combination therapy with another antidepressant in expectation of synergistic or additional therapeutic benefits in treating depression. Timmerman (chapter 9, E J of pharmacology, 181, 1989, 253-60) teaches N-0437 (rotigotine) as an antipsychotic drug. Hrdlicka teaches combination of clozapine and maprotiline (a tricyclic antidepressant) in refractory psychotic depression treatment Rotigotine is known in the art as D2 dopamine agonist and a promising candidate for psychotherapeutic use and also known to be an anti-psychotic drug. It would have been obvious to one having ordinary skill in the art at the time of the invention to have used rotigotine in combination

with an anti-psychotic in treating depression because it is known in the art that antipsychotics have been used in a combination therapy along with an antidepressant in treating depressive disorders. Kupfer teaches that depressed patients often report problems sleeping and epidemiologic evidence suggests that insomnia may precede the onset of depression (see Abstract). One having ordinary skill in the art would have been motivated to use a sedative agent along with an antidepressant in combination therapy in treating depressive patients is to help the patients and improve the quality of sleep in the patients. It is known in the prior art that risk of migraine in individuals with pre-existing major depression was three times higher than in individuals with no history of depression and the risk of major depression in persons with pre-existing migraine was more than fivefold higher than in people with no history of headaches. One having ordinary skill in the art would have been motivated to use an anti-migraine agent along with an antidepressant in combination therapy in treating depressive patients to provide therapeutic benefits for migraine.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the modified rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627